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(54) Slow-release topical formulations.

(57) Salts of 2,4-diamino-6-piperidino-pyrimidine-3-oxide (minoxidil) with hydrosoluble polyanions such as polystyrenesulfonates, polyacrylates, polyphosphates, polyvinylsulfonates, sulfates or phosphates and polydextransulfates are described.

The salts according to the invention, prepared by precipitation from aqueous solutions having pH generally lower than 4.5, show chemico-physical characteristics supporting an advantageous use as slow-release active principles, in topical pharmaceutical compositions endowed with higth coating potency, of occlusive kind, to be used in the prevention and treatment of alopecia and of hair loss.

EP 0 211 268 A2

SLOW-RELEASE TOPICAL FORMULATIONS

The present invention concerns new 2,4-diamino-6-piperidino-pyrimidine-3-oxide (minoxidil) salts with hydrosoluble polyanions, processes for the preparation thereof and the therapeutic formulations containing them as the active principle.

The 2,4-diamino-6-piperidino-pyrimidine-3-oxide, commonly known as minoxidil, is a synthetic drug exerting a remarkable vasodilating action. Because of this pharmacological activity the compound is used since 10 years in form of oral formulations in the treatment of resistant hypertensions of any etiology. A drug side-effect is the onset of hypertricosis phenomena in the almost totality of the treated subjects, independently from the age and sex.

In a series of recent publications (Fenton D.A. et al., J. Royal Soc. Med. 75, 963, 1982; Fenton D.A. et al., British Med. J. 287, 1015, 1983; Weiss V.C. et al., Acta Derm. 120, 457, 1984; Wester R.C., J. Invest. Dermatol. 82, 515, 1984; Weiss V.C. et al., J. Invest. Dermatol. 82, 90, 1984), the effectiveness of the topical use of minoxidil for the therapy of different forms of alopecia has been widely documented.

Although the mechanism of the minoxidil induced hypertricosis is not known in detail, according to one of the most qualified theories, the new growth of the hair seems to be the consequence of an increase of the blood flow at the follicles, connected with the potent vasodilating action of minoxidil.

More recently, it has been shown that the drug acts also as an immunomodulating agent, existing a correlation between the minoxidil treatment and the appearance of perifollicular infiltrates in the cutis area affected by the alopecia.

In the treatments up to now tested, the active principle, dissolved in ternary systems comprising ethanol, isopropanol and water, or dispersed in ointments, is applied on the skin.

The achievement of positive results is connected with:

1) systematic treatments so as to make continuously available the active principle (the present formulations require 3-4 applications per day);

2) long duration of treatment, ranging from 3 to 6 months, according to the kind of the used formulations;

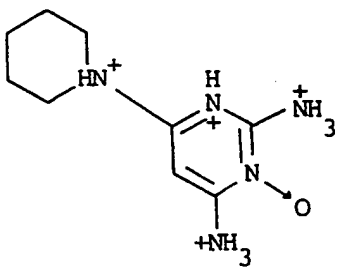
3) preparations of occlusive kind, providing therapeutic effects in shorter times.

On the ground of said experimental findings, an occlusive formulation of minoxidil, able to gradually release, at the skin level, the active principle, represents an ideal solution.

Said formulation would in fact allow the reduction of the applications' frequency, providing in the same way a continuous availability of the active principle in optimal concentrations to exert the action at the cutaneous level on the hair follicles but avoiding contemporaneously undesired hypotensive effects due to the fast absorption and to the high vasodilating activity of the drug, the latter being the most serious obstacle to a wide use of the drug in the treatment of alopecia.

It has now been found that the minoxidil salts with hydrosoluble polyelectrolites of the anionic kind are endowed with advantageous characteristics, so as to make them particularly suited to the use as slow-release, topical drugs of occlusive kind, with high coating potency, to be used in the treatment or prevention of alopecia or of hairs loss.

The charge state of minoxidil, controlling its water solubility, depends on the medium's pH, because more sites which can be protonated are present in the molecule. At neutral pH, the hydrophobicity of minoxidil is high and its water solubility is extremely low; in acidic media up to pH 4.5, minoxidil is on the contrary very soluble, because it behaves as a polycation, having, according to the medium acidity, up to 4 positive charges, as shown in the following formula:



The charge state and the structural peculiarities of minoxidil in aqueous solution at pH up to 5, are such as to provide a stable and specific interaction of th molecule with the negatively charged sites of hydrosoluble polyelectrolites of anionic kind. Consequence of said interaction is the formation of slightly soluble or soluble salts, characterized by a low value of the dissocia tion constant.

The stoichiometry of said salts depends from more factors such as: a) the minoxidil-polyanion ratio used in the reaction; b) the pH and the kind of the reaction medium; c) the chemical nature of the polyanion. Generally, the preparation of slightly soluble salts is carried out using minoxidil-polyanion equivalents ranging from 1 to values even lower than 0.1. The stoichiometry of said salts with respect to a given polyanion is a function of the pH of the precipitation step.

If, for instance, the polyanion is a strong acid, pH increases up to 4.5 cause an increase of the minoxidil moles-polyanion equivalents ratio in the salt. The electroneutrality of the precipitated salt is provided by the presence of anions and cations in the reaction medium.

A large number of said salts may be dissolved again provided that further polyanion is added in the reaction medium. Said behaviour, typical of slightly soluble salts of polyelectrolites with multiple charge ions, clearly differentiates said class of compounds from the conventional slightly soluble salts, wherein the addition of a common ion decreases the solubility.

The minoxidil soluble salts with polyanions are poorly dissociated and the minoxidil cations firmly interact in water with the negatively charged macromolecule, because of the high cooperation of the electrostatic interactions and the particular situation of the microenvironment on the surface of the uniformely negatively charged polyanion.

In aqueous medium, the soluble and insoluble mino xidil salts with polyanions are characterized by the achievement of equilibrium conditions in which the active principle is mainly present in a form bound to the polyanion and only to a small extent as dissociated ion. In systems wherein the free ion is continuously removed from the equilibrium, as in the case of cutaneous absorption of the drug, a continuous displacement towards the dissociation of the minoxidil-polyanion salt occurs. In other words, the complex behaves like a slow-release system, controlled under the kinetic profile by the characteristics of the absorption process, which in any case may not directly influence the minoxidil-polyanion salt because of the high molecular weight of said compound.

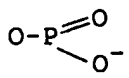
A direct experimental evidence of the slow-release mechanism, characterizing the minoxidil-polyanion salts, is obtained by dialysis equilibrium tests, as shown in the enclosed Figure. Using dialysis membranes impermeable to the polyanion and to the salt thereof with minoxidil, an equilibrium between free and polyanion bound minoxidil is obtained after a while. If the dialysis solution is substituted, the equilibrium is recovered after dissociation of a further amount of salt. This process mimicks "in vitro" the drug's slow release action at the skin level, characterized by a constant and uniform absorption of the active principle, whose availability in time is provided by the continuous dissociation of the salt.

The topical use of the minoxidil hydrosoluble salts with polyanions is extremely advantageous, because the high viscosity and adhesivity of the macromolecules causes a remarkable coating power of the preparation, adhering firmly on the skin, giving thereby rise to long-lasting applications of the occlusive kind.

The structural identity of the polyanions and its molecular weight are the parameters by which the optimization of the coating power of the active principle can be regulated with continuity. Said parameter is extremely important for the pharmacological action, having been already shown that occlusive formulations give therapeutic result in shorter period of times.

The use of the slightly soluble minoxidil salts with polyanions involves, on the other hand, the use of suitable carrier systems.

Generally, minoxidil salts with polyanions are prepared from strong or weak polyacids. Examples of polyanions deriving from strong acids are polymers or copolymers containing in the macromolecular backbone, recurrent $-SO_3^-$ groups - (polyethylenesulfonate, polystyrenesulfonate, etc.), OSO_3^- groups (polyvinylsulfate, polydextransulfate, etc.), $O-PO_3^=$ and $O-PO_3H^-$ groups - (polyvinylphosphate , etc.),



(polyphosphates, metaphosphates, etc.). Examples of polyanions deriving from weak polyacids are polymers or copolymers containing -COO⁻ groups (polyacrylates, polymethacrylates, carboxymethylcellulose, polygalacturonates, etc.). As far as the polyanion molecular weight is concerned, the formation process of the salt is not critically controlled by said parameter.

It is in fact generally observed that each polyanion may form in acidic medium minoxidil salts poorly dissociated in a wide range of molecular weights, range which has an upper limit in the polyanion hydrosolubility and a lower limit in a polymerization degree sufficient to classify the molecule as a polyelectrolite (Doty P. et al. in "Polymeric Electrolytes", Ann. Rev. Phys. Chem. 3, 81, 1952).

The formation of minoxidil salts with polyanions is carried out by adding to acidic minoxidil solutions (preferred pH from 2.0 to 4.5) a solution of the polyanion at the same pH, till the maximum degree of precipitation is obtained. The addition of further amounts of polyanions generally causes the dissolution of the precipitate, with the formation of the poorly dissociated soluble salt.

It is possible to carry out the precipitation of minoxidil from extremely diluted (<1 mM) solutions, but the process is preferably carried out with concentrations ranging from 2 to 200 mM.

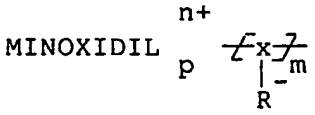
The stoichiometry of the slightly soluble minoxidil salts with a certain polyanion may be changed in a certain interval according to the pH of the medium wherein the precipitation is carried out.

The stoichiometry of the poorly dissociated soluble salts depends on the excess of polyanion added in order to solubilize again the precipitate.

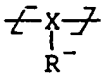
The formation of the two kinds of salts, insoluble and soluble, may also be carried out adding the minoxidil solution to that of the polyanion.

In this case, the poorly dissociated soluble salt, characterized by the higher value of the ratio minoxidil moles/polyanion equivalents, is obtained by quenching the reaction when the formation of the precipitate, at the given pH, begins; further additions of minoxidil cause the quantitative precipitation of the salt.

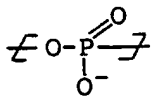
The pH of the solutions of the minoxidil salts with polyanions may be represented by the following formula:



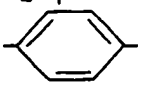
wherein n is ranging from 1 to 4 as a function of the precipitation pH and, by way of an example, the group



may represent a group of formula



(polyand metaphosphates),

or $\left(-X-\right)_n$ may represent a groups of formula $\left(-CH_2-\underset{|}{CH}-\right)_n$ or $\left(-\underset{|}{sugar}-\right)_n$ and R one of the following groups  , $-SO_3^-$, $-SO_3^-$, $-OSO_3^-$, $-OPO_3H^-$, COO^-.

When the preparation of the salt yields a stoichiometry wherein np≠m, anions or cations in the medium contribute to the maintaining of the salt electroneutrality.

The process described in the present invention, for their convenience and low costs, are particularly suited to the application on industrial phase.

The compounds of the present invention may be formulated in topical, pharmaceutical and cosmetic compositions, using conventional excipients and techniques.

By way of an example, the salts object of the invention may constitute the active principle of ointments, lotions, creams, shampoos, gels, sprays, balsams and the like, containing suitable carriers and excipients such as detergents, surfactants, parfums, preserving agents, colours etc. The concentration of the active principle, expressed as minoxidil, ranges from 1 to 10% by weight.

The compositions according to the invention wil be usually administered once a day, allowing a continuous and controlled release of the active principle, with increased effectiveness in comparison with conventional formulations.

The following examples further illustrate the invention without limiting it in any way.

EXAMPLE 1

209 Grams of minoxidil are suspended in 20 liters of distilled water. Under stirring, HCl 1M is added till complete dissolution of minoxidil, taking care that the final pH is 3.5. Water is added up to 25 liters so as to have a resulting 40 mM minoxidil solution. Under strong stirring, this solution is gradually added to 7.5 liters of a 0.4N solution of sodium polyparastyrenesulfonate (Mw 7 x 10^4), whose pH has been adjusted to 3.5 (the equivalent weight of the polyanion is 183).

The UV spectrum of the solution presents a maximum at 283 nm, characteristic of minoxidil (molar ϵ = 14,700), while at lower wavelenghts the second absorption maximum of minoxidil (229 nm, molar ϵ = 29,000) overlaps with the absorption spectrum of the benzene cromophore of the polyanion. The ^{1}H-NMR spectroscopy (^2H_2O; pH 3.5) of the poorly dissociated salt of minoxidil with polyparastyrenesulfonate shows respectively, in th correct integration ratio, the polyanions signals centered at δ 7.5 (6H; H 3 and 5 on the benzene ring); 6.5 (6H; H 2 and 6 on the benzene ring); 1.4 (9H; -C<u>H</u>$_2$-C<u>H</u>) and those of minoxidil at δ 3.0 (2H; H 2' and 6'); 1.2 (1H; H 4'); 1.1 (2H; H 3' and 5'). In the used experimental conditions the proton in 5 on the aromatic ring completely exchanges with the deuterated solvent and the signal is therefore not visible in the ^{1}H-NMR spectrum. Said spectroscopical pattern clearly shows that, in solution, the minoxidil salt with polyparastyrenesulfonate is present in non-dissociated form; the signals of the cation, in fact, analogously to what occurs for the polyanion, lose the multiplicity belonging thereto and appear as broad signals, shifted of 0.25 δ at higher fields with respect to the signals of minoxidil chloride at the same pH. The spectroscopical characterization (UV and ^{1}H-NMR) of the UV-absorbing material crossing the dialysis membrane (cut-off limits ~10,000) shows that it is made up of minoxidil ion. The so prepared solution of minoxidil with polyparastyrenesulfonate is remarkably viscous and the identity of the salt remains indefinitely unchanged at room temperature.

EXAMPLE 2

The same process described in Example 1 is carried out, using polyparastyrenesulfonate having molecular weight 6 x 10^6. The spectroscopical characterization of the obtained salt and its behaviour in equilibrium dialysis tests are similar to what reported in the Example 1; the only observed difference is an higher viscosity of the solution of the salt.

EXAMPLE 3

The same process as described in Example 1 is carried out, but the pH of the minoxidil and polyparastyrenesulfonate solutions is 4.4. The spectroscopical characterization of the salts obtained and its behaviour in equilibrium dialysis are similar to what reported thereinaf ter.

EXAMPLE 4

69.7 Grams of minoxidil are suspended in 1.5 liters of distilled water. Under stirring, 1M HCl is added till complete dissolution of minoxidil, taking care that the final pH of the solution is 2.4. Water is added up to 2 liters so that the resulting solution has a concentration of 167 mM. Under strong stirring, 0.5 liters of 1.3N sodium polyparastyrene sulfonate (Mw 5 x 10^5) solution, whose pH has been adjusted to 2.4 (the equivalent weight of the polyanion is 183), are slowly added to said solution. The formation of a milky emulsion is immediately noticed, which has a tendency to coagulate, giving a dense white precipitate which can be recovered by decantation of the solution. After washing with H_2O, the precipitate is dried under vacuum, giving 175 g of a white crystalline, non-hygroscopic product, which is finely triturated.

The precipitate, suspended again in 0.5 liters of 0.66N sodium polyparastyrenesulfonate, is easily solubilized, yielding the poorly dissociated salt, whose spectroscopical characterization (UV and ^{1}H-NMR) and behaviour in equilibrium dialysis experiences are similar to what reported in the Example 1.

Said equilibrium dialysis experience, directly carried out on the suspension of the salt, analogously to what hereinafter exemplified, demonstrate the existence of an equilibrium between minoxidil ion in solution and minoxidil bound to polyanion.

EXAMPLE 5

627 Grams of minoxidil are suspended in 25 Liters of distilled water. Under stirring HCl 2N is added up to complete dissolution of minoxidil, taking care that the final pH of the solution is 4.4. Water is added up to 30 liters so that the concentration of minoxidil in the final solution is 0.1N. Under strong stirring, 10 liters of a 0.3N sodium parapolystyrenesulfonate (Mw 5 x 10^5) solution, pH 4.4 is slowly added to said solution. The formation of a white precipitate which can be removed by decantation is observed.

After washing with water, the precipitate is dried under vacuum giving 1.045 g of a white crystalline solid. The precipitate, suspended again in 20 liters of a solution 0.3N pH 4.4, is easily dissolved, yielding the poorly dissociated salt, whose spectroscopical characterization (UV and ^{1}H-NMR) and behaviour in dialysis equilibrium are analogous to what reported for the Exampl 1. Experiences of equilibrium dialysis, carried out on the salt suspension, show the existence of an equilibrium between minoxidil and minoxidil bound to the polyanion.

EXAMPLE 6

104 Grams of minoxidil are suspended in 9 liters of distilled water. Under stirring HCl 1N is added up to complete dissolution of minoxidil, taking care that the final pH of the solution is 4.4. Water is added up to 10 liters so that the concentration of minoxidil in the final solution is 50 mM. Under strong stirring, 1.5 liters of a 1N sodium polyacrylate (Mw 2.5 x 10^5) solution, whose pH has been adjusted to 4.4 (the equivalent weight of the polyanion is 71). A white precipitate which can be removed by decantation is obtained.

After washing with water, the precipitate is dried under vacuum giving 190 g of a white crystalline solid which is finely triturated. The spectroscopical characterization (UV and ^{1}H-NMR) of the UV-absorbing material crossing the dialysis membrane (cut-off limits ~10,000) shows that it is made up of minoxidil ion, while the solution remaining up stream with respect to the membrane is made up by polyacrylic acid, as shown by ^{1}H-NMR spectroscopical data showing, in the correct integration ratios at 1.8 and 2.2 δ, in form of broad signals respectively the methylene and methine groups in the polymeric chain.

EXAMPLE 7

10.4 Grams of minoxidil are suspended in 0.9 liters of distilled water. Under stirring, HCl 1M is added till complete dissolution of minoxidil, taking care that the final pH is 3.2. Water is added up to 1 liter so as to have a resulting 50 mM minoxidil solution. Under strong stirring, this solution is slowly added to 1 liter of a 0.1N solution of hexametaphosphate, pH 3.2 (the equivalent weight of the polyanion is 79). A viscous precipitate, which is recovered by decantation, is obtained.

After washing with H_2O and drying under vacuum, 12 g of a white crystalline solid are obtained. Equilibrium dialysis tests carried out on the salt suspension show the existence of an equilibrium between the minoxidil ion and the polyanion found minoxidil.

EXAMPLE 8

20 Grams of minoxidil are suspended in 9 liters of distilled water. Under stirring, HCl 1N is added till complete dissolution of minoxidil, taking care that the final pH is 4.4. Water is added up to 10 liters so as to have a resulting 0.1N minoxidil solution. Under strong stirring, this solution is gradually added to 5 liters of a 1N solution of sodium polydextransulfate (Mw 5 x 10^5), whose pH has been adjusted to 4.4 (the equivalent weight of the polyanion is 257). The UV spectrum of the solution presents a maximum at 283 nm, characteristic of minoxidil (molar ϵ = 14,700), and at 229 nm (molar ϵ = 29,000). The ^{1}H-NMR spectroscopy (^2H_2O; pH 4.4) of the soorly dissociated salt of minoxidil with polydextransulfate shows respectively, in the correct integration ratio, the polyanions signals in the δ 3.0-6.0 (30 M) and those of minoxidil at δ 3.0 (2H; H 2' and 6'); 1.2 (1H; H 4'); 1.1 (2H, H 3' and 5'). Said spectroscopical pattern clearly shows that, in solution, the minoxidil salt with polydextransulfate is present in non-dissociated form. Equilibrium dialysis tests carried out on the salt suspension show the existence of an equilibrium between the minoxidil ion and the polyanion found minoxidil.

EXAMPLE 9

In Figure 1, the moles of minoxidil ion recovered in the dialysis water are removed. 10 ml of a solution containing 0.45 mmoles of minoxidil chloride at pH 4.4 (—— Δ ——) or of the poorly dissociated minoxidil salt with polyparastyrenesulfonate (Ex. 1, Mw 7 x 10^4, stoichiometry 1:3 minoxidil moles:polyanion equivalents) at pH 4.4. (—— ▲ ——) and 10 ml of a fine suspension containing 0.45 mmoles of the slightly soluble minoxidil salt with polyacrylate (Ex. 6, Mw 2.5 x 10^5, stoichiometry 1:3 minoxidil moles:polyanion equivalents) at pH 4.4 (—— • ——) are equilibrated through a dialytic barrier with 130 ml of water at pH 4.4.

When the equilibrium conditions are reached at the points marked by the arrows, the equilibrium solution is removed, substituting it with 130 ml of water, till reestablishment of the new equilibrium conditions. While the minoxidil chloride solution reaches rapidly the equilibrium and about 90% of minoxidil is found outside the dialysis membrane, in the case of the polyanion salts the equilibrium is characterized by the output through the membrane only of a portion of the minoxidil ion, while the remaining porti n remains fixed, according to the laws of the chemical equilibrium, in the not permeable, undissociated form.

The complete mobilization of the minoxidil ion from the polyanion salt asks for the continuous removal of the minoxidil ion from the equilibrium, as it occurs in the preceeding experiment, by substituting the equilibrium solution with water and, in the case of the topical administration of the drug, by the cutaneous absorption of the active principle.

The obtained results clearly show the existence of an equilibrium in the dissociation of the minoxidil salt with the polyanion.

EXAMPLE 10

2% Minoxidil solution

Minoxidil polystryrensulfonate (M.W. 7 x 10^4) 7.892 g

NaOH 1N0.8 ml

Nipagine 0.1 g

Nipasol 0.04 g

Distilled H_2O q.s. to 100 ml.

EXAMPLE 11

2% Minoxidil solution

Minoxidil polystyrensulfonate (M.W. 6 x 10^5) 7.621 g

NaOH 1N 0.8 ml

Nipagine 0.1 g

Nipasol 0.04 g

Distilled H_2O q.s. to 100 ml.

EXAMPLE 12

6% Minoxidil solution

Minoxidil polystyrensulfonate (M.W. 7 x 10^4) 23.676 g

NaOH 1N 2.0 ml

Nipagine 0.1 g

Nipasol 0.04 g

Distilled H_2O q.s. to 100 ml.

EXAMPLE 13

6% Minoxidil solution

Minoxidil polystyrensulfonate (M.W. 6 x 10^5) 22.863 g

NaOH 1N 2.0 ml

Nipagine 0.1 g

Nipasol 0.04 g

Distilled H_2O q.s. to 100 ml.

Claims

1. 2,4-Diamino-6-piperidino-pyrimidine-3-oxyde (minoxidil) salts with polyanions containing on the polymeric structure strong or weak acid groups.

2. 2,4-Diamino-6-piperidino-pyrimidine-3-oxyde (minoxdil) salts according to claim 1, characterized in that the polyanions are selected in the group consisting of polyphosphate, metaphosphates, polystyrenesulfonates, polyvinylsulfonates, polyvinlysulfates, polyvinylphosphates, polyacrylates, polymetacrylates, polydextransulfates.

3. 2,4-Diamino-6-piperidino-pyrimidine-3-oxyde (minoxidil) salts according to claim 1 or 2, characterized in that the stoichiometric ratio is ranging from 0.1 to 1.0 moles minoxidil/equivalent-gram of polymer.

4. Slightly soluble salts of 2,4-diamino-6-piperidino-pyrimidine-3-oxyde (minoxidil) according to claims 1-3, obtainable by precipitation in acidic room with the polyanions.

5. Soluble, poorly-dissociated salts of 2,4-diamino-6-piperidino-pyrimidine-3-oxyde (minoxidil) according to any one of claims 1, 2 or 3, obtainable by solubilization by means of addition of an excess of polyanion to the salts prepared according to claim 4 or by means of addition of a minoxidil acidic solution to a polyanion solution, in the range of the stoichiometric ratios not involving the precipitation.

6. Process for the preparation of the salts of claims 1-4, by precipitation of minoxidil with hydrosoluble poly anions, characterized in that a minoxidil solution having an acidic pH is mixed, under stirring and at room temperature, with a polyanion solution at the same pH and that the obtained precipitate, recovered by decantation, filtration or centrifugation, is washed with water and dried by evaporation under vacuum or lyophilization.

7. Process for the preparation of the salts of claim 5, characterized in that a solution of the polyanion, at a given pH, is added to a minoxidil acidic solution at the same pH, kept under stirring at room temperature, up to the complete dissolution of the precipitate.

8. Process for the preparation of the salts of claim 5, characterized in that a solution of the polyanion, at a given pH, is added to a minoxidil acidic solution at the same pH, kept under stirring at room temperature, interrupting the addition before of the formation of the precipitate.

9. Pharmaceutical and cosmetic compositions containing as active principle at least one of the salts of claims 1-5, in addition to possible non-toxic, suitable excipients.

10. Pharmaceutical and cosmetic compositions according to claim 9, suited for the topical administration in form of lotion, ointment, spray, shampoo, cream, balsam, solution.

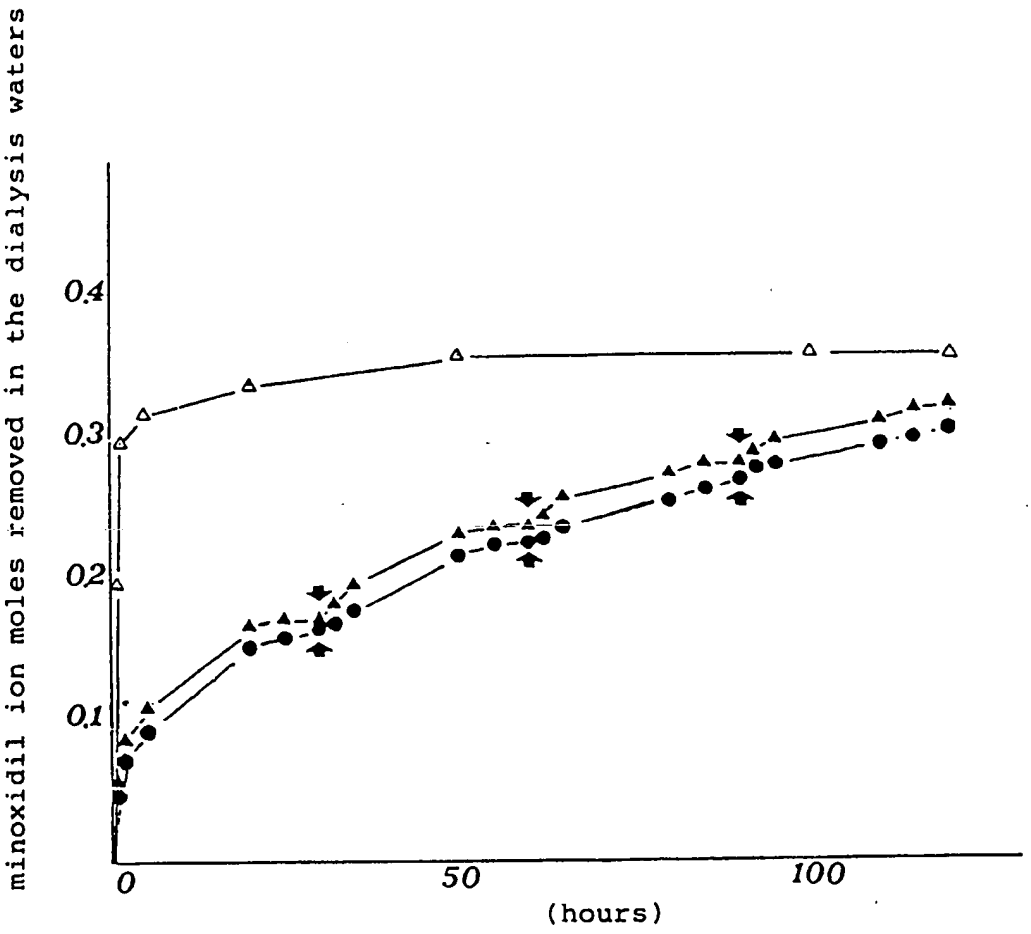
CLAIMS FOR CONTRACTING STATE: AT

1. A process for the preparation of 2,4-diamino-6-piperidino-pyrimidine-3-oxide (minoxidil) salts with polyanions containing on the polymeric structure strong or weak acid groups by precipitation of minoxidil with hydrosoluble polyanions, characterized in that a minoxidil solution having an acidic pH is mixed, under stirring and at room temperature, with a polyanion solution at the same pH and that the obtained precipitate, recovered by decantation, filtration or centrifugation, is washed with water and dried by evaporation under vacuum or lyophilization.

2. A process for the preparation of soluble, poorly dissociated salts of 2,4-diamino-6-piperidino-pyrimidine-3-oxide (minoxidil) characterized in that a solution of the polyanion, at a given pH, is added to a minoxidil acidic solution at the same pH, kept under stirring at room temperature, up to the complete dissolution of the precipitate.

3. A process for the preparation of soluble, poorly dissociated salts of 2,4-diamino-6-piperidino-pyrimidine-3-oxide (minoxidil) characterized in that a solution of the polyanion, at a giv n pH, is added to a minoxidil acidic solution at the same pH, kept under stirring at room temperature, interrupting the addition before of the formation of the precipitate.

4. A process for the preparation of 2,4-diamino-6-pi-peridino-pyrimidine-3-oxide (minoxidil) salts with polyanions wherein the polyanions are selected in the group consisting of polyphosphate, metaphosphates, polystyrene sulfonates, polyvinylsulfonates, polyvinylsulfates, polyvinylphosphates, polyacrylates, polymetacrylates, polydextransulfates.


minoxidil ion moles removed in the dialysis waters
0.4
0.3
0.2
0.1
0
50
100
(hours)